February 28, 2001

National Human Research Protection Advisory Committee (NHRPAC)
ATTN: Dr. Greg Koski
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Dear Dr. Koski:

I am writing on behalf of the University of Wisconsin-Madison to respond to the draft Interim Guidance on Financial Relationships in Clinical Research.

We concur with OHRP that the growing number of financial relationships between investigators and corporate entities can introduce conflicts of interest which could adversely effect scientific objectivity and undermine public trust. Identification and management of potential conflicts of interest are therefore essential for maintaining the public's confidence in the integrity of scientific investigations.

We also agree that conflicts of interest in clinical research warrant particular scrutiny because of the involvement of human subjects. However, it is also important to acknowledge that the existence of potential conflicts of interest should not automatically disqualify investigators or institutions from participation in clinical studies, nor should it be considered sufficient grounds to prohibit conduct of research. Rather, it is incumbent on the institution and individual investigators to make certain that potential conflicts are identified, evaluated and, if appropriate, managed prior to initiation of clinical studies. In such cases, the objective of all parties involved should be preservation of the delicate equilibrium between the reporting and oversight of individual investigator's outside financial interests and the encouragement of clinical studies offering potential biomedical advances which could benefit patients. Our responses to the Interim Guidance document are predicated on this fundamental operating principle.

1. The Institution: Institutional Considerations

1. We agree with the recommendation that institutions should collect information about significant financial interests of investigators involved in clinical studies as well as from the IRB staff, Chair and members (Section 1.4). However, disclosure should to be limited to those financial interests exceeding predetermined thresholds. Threshold levels should be decided after consideration of input from, and discussion among, various stakeholders. In the interim, adoption of existing PHS and NSF definitions of

.2 "significant financial interests" would make this policy consistent with other federally-mandated disclosures. The absence of a threshold would result in either an extraordinarily burdensome system, whose costs would be disproportionate to benefits. It is important that regulations be perceived as reasonable by those who are expected to comply with them.

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Evaluation of conflicts of interest involves many unique and complex challenges. Appropriate oversight is best accomplished by an institutional body with expertise in dealing with these complicated relationships. We therefore support OHRP's recommendation that conflict of interest issues related to clinical studies be relegated to the institution's Conflict of Interest committee. Such delegation would also ensure that already over-burdened IRBs would not be subjected to further obligations. However, the IRBs should be authorized to impose specific conditions which in their judgement are deemed necessary to provide for the protection of human subjects before any protocol is approved.

Success of this process of shared responsibility is dependent on the existence of mechanisms ensuring that decisions related to individual potential conflicts of interest and participation in clinical studies are effectively shared by all relevant institutional committees and offices. We therefore also endorse OHRP's recommendations that an effective system of communication among these oversight committees be established at the institutional level.

1.3 While the possibility that institutional conflicts of interest might exist when an institution has a financial stake or other interest in the outcome of the research, we believe the magnitude of the risk as implied in the interim document is grossly overstated. The suggestion that research institutions systematically exert undue influence on IRB decisions affecting their financial interests is likewise exaggerated in our experience. We therefore disagree with OHRP's suggestion that "broad participation of members from outside the institution" is required to relieve what amounts to a non-problem. Proposal of such a remedy also fails to acknowledge the numerous problems incumbent in the large scale recruitment of independent participants for such intense, time-consuming and specialized service.

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1.7 Research institutions should, of course, be cognizant of the potential threat that their institutional financial relationships might pose and should be proactive in implementing appropriate control measures, including some of those suggested in Section 1.6 and 1.7. However, we contend that this has always been the case at the University of Wisconsin and at our peer institutions. Even in cases in which additional oversight is desirable, we disagree with OHRP's contention that advisory and oversight committees appointed for this purpose need be comprised largely of individuals having no relationship to the institution.

1. Clinical Investigators

All clinical investigators should participate in educational and training opportunities (Section 2.3) and should be able to recognize how their personal financial relationships with external entities might exert real or perceived influences on the design, conduct or reporting of clinical investigations in which they participate (Section 2.1). However, the ultimate decision about the extent of participation in a particular study should remain the responsibility of the Conflict of Interest committee and the IRB operating collaboratively (Section 2.2). Their decision should be predicated on the financial information provided by the investigator.

1. IRB Members and Staff

We agree in principle with the operating standards articulated in Section 3.1 to 3.3, but note that Section 3.1 is more operational in tone than necessary. While perhaps most apparent at this section, much of the guidance document includes language which is more prescriptive than optimal for a guidance document. OHRP's document should provide general guidance, leaving decisions regarding implementation to individual institutions.

1. IRB Review of Protocols and Approval of Consent Documents

We support disclosure of relevant financial issues to the IRB for their consideration in review and approval of associated research protocols. As stipulated earlier, determination of whether a conflict of interest exists should be made by the Conflict of Interest committee and shared with the IRB, which in turn should be responsible for determining whether specific protocols are acceptable or whether specific conditions, including the need to make disclosures in the consent document, must be imposed. However, disclosure of financial interests in consent documents should not be an automatic requirement for approval of protocols directed by faculty having any financial interests. Rather, the IRB should exercise discretion and judgement in determining when such action is necessary in individual cases. A requirement to disclose all financial interests could be interpreted to require detailed disclosure of the complex salary structure of clinical investigators. This would necessitate lengthening of already-long consent forms with detailed information of little relevance to most potential subjects.

The list of items for IRB consideration included in Section 4.3 provides a useful guide to issues that IRBs should collect and consider during protocol review. Information about Conflict of Interest committee actions and the terms of any applicable management plans should also be included in this dataset.

1. Consent

In some cases, it is likely that disclosure of individual or institutional financial

arrangements with sponsors of a particular study during the consent process would be necessary to ensure protection of subjects. Therefore, we agree that institutions should consider inclusion of such information in relevant consent documents. However, as mentioned already, this should not be construed as a pre-requisite for any and all protocols involving potential conflicts of interest. Determination of whether such disclosure is necessary or in the best interest of study participants should be the responsibility of the IRB. The IRB should also determine the most effective means of ensuring that prospective participants receive an objective, unbiased description of the research and their role in it. This may or may not involve the use of an impartial third party to conduct the consent process.

Potential conflicts of interest, real or perceived, can indeed pose a threat to the objectivity of scientific research and can jeopardize public trust. This is particularly troublesome when the research in question involves the participation of human subjects. However it is important to note that public trust can also be eroded by creating false impressions of rampant problems. While acknowledging that problems can exist, we must avoid endorsing the notion that the exceptional is actually typical.

Additional precautions to ensure protection of participants in clinical studies are well justified; indeed, are essential. However, we believe that any recommended responses to possible conflicts of interest in clinical studies must avoid inflexible absolutes. We would advocate a system in which facts relevant to individual protocols be assessed by the appropriate institutional oversight committees when deciding appropriate measures to protect human subjects of research. Only a flexible system relying on the judgement of local Conflict of Interest committees and IRBs can preserve the important balance required to protect participants in research while encouraging the conduct of trials to advance the treatment of disease. We believe that without substantive revision, the Interim Guidance document will fall short of this ideal.

Finally, promulgation of specific recommendations on this topic, even though expressed in the form of a guidance document, seems premature as its posting predates publication of recommendations from numerous professional organizations, such as the AAU, COGR and the AAMC, which are in the process of developing their own recommended standards addressing this issue. We therefore recommend that OHRP postpone further action on the Interim Guidance document until the recommendations from these and other organizations have also been publicized and considered.

In the interim, OHRP should continue to encourage dialogue on this important and sensitive issue. We look forward to participating in such deliberations and are appreciative of the opportunity to respond to the positions presented in Interim document.

Sincerely,

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